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| EXAMINER | |
|---|---|
| HAGHIGHATIAN, MINA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1616 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/735,959 | DRECHSEL ET AL. | |
| | Examiner | Art Unit | |
| | MINA HAGHIGHATIAN | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02/13/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14,16,18-20,22-31,38-66,68 and 70-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16,18-20,22-31,38-66,68 and 70-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/24/09 and 03/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/13/09 has been entered.

Receipt is acknowledged of the Amendments and Remarks filed on 02/13/09, and IDS filed on 02/24/09 and an IDS filed on 03/27/09. Claims 1 and 53 have been amended and no claims have been cancelled or newly added. Accordingly, claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** remain pending.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al (DE 19653969 as evidenced by US 2001/0008632) in view of Freund et al (WO9701329 as evidenced by US 6,491,897).**

Freund et al '632 teach pharmaceutical preparations in the form of **aqueous solutions** for the production of propellant-free aerosols for inhalation for the therapy of obstructive lung diseases. Pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution or a **solvent mixture of ethanol and water**. The amount of dissolved pharmaceutical in the preparation is **between 0.001 and 30%,** and preferably between 0.05 and 3%. All substances which are suitable for application by inhalation and which are soluble in the specified solvent can be used as pharmaceuticals in the new preparation. Of especial interest are betamimetics, anticholinergics, antiallergic, antihistamines and steroids, as well as combinations of these active ingredients (sections [0001] to [0007]).

Freund et al '632 teaches that addition of an effective amount of a complexing agent, such as, **EDTA, citric acid, ascorbic acid and their salts**, and more especially disodium salt of ethylenediaminetetraacetic acid, eradicates the problem of spray anomalies. The effective quantity of complexing agent Na-EDTA is between 10 and 100

mg/100 ml. Also if necessary, ethanol can be added to increase solubility up to 70% by volume. Other adjuvants such as preservatives, especially benzalkonium chloride can be added in amounts of between 8 and 12 mg/100 ml (sections [0009] to [0013]).

Freund et al '632 discloses a list of compounds which can be used as active ingredients, singly or in combination, in the aqueous pharmaceutical preparation. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility. The list includes; **tiotropium bromide**, budesonide, beclomethasone, disodium cromoglycate, etc. The solutions are set to a pH of 3.2 to 3.4 with 0.1 or 1 N **HCL** in 100 ml of finished preparation (see sections [0014] to [0046] and [0055]). Freund et al '632 does not specifically disclose pH levels of 2.0 to 3.0.

Freund et al '897 teach a stable ethanolic solution of budesonide suitable for nebulization (see abstract). The formulation may further comprise other active agents such as tiotropium bromide (col. 2, lines 6-49). The formulation preferably has a pH of from 2 to 7, adjusted by the amount of an acid such as hydrochloride acid (see col. 2, lines 60-67). In a preferred embodiment, the formulations comprise a quantity of a complexing agent, preferably EDTA, from about 0.1 to about 3 mg/100 mL (col. 3, lines 1-15)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations of Freund et al '632 comprising tiotropium, solvent, an acid, EDTA and other additives such as benzalkonium chloride

by implementing the teachings of Freund et al '897 on lower amount of EDTA and lower pH levels, with a reasonable expectation of successfully preparing safe and stable formulations. In another word, the claims would have been obvious because the technique for improving a particular product was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. In this situation the improvement is lowering pH levels. One of ordinary skill is well aware that by adjusting the concentration of the acid the pH levels would be adjusted. Freund et al '632 teach that low pH levels are suitable for the said formulations, and one could further lower the pH levels to test for stability.

**Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jager et al (WO 9413262) in view of Bozung et al (DE 19921693 as evidenced by US patent 6,433,027).**

Jager et al teach stabilized medicinal aerosol solution formulations comprising medicaments that degrade or decompose by interaction with solvents or water. The most preferred examples of the medicaments for use in the aerosol solution formulations include ipratropium bromide, **tiotropium bromide** and fenoterol hydrobromide (see page 8, lines 3-9). Suitable solvents include ethanol and water (see pages 9-10 and examples). One or more acids are added to effect the rate of degradation of the medicament and adjust the pH. Such acids include inorganic acids such as hydrochloric acid and nitric acid or organic acids such as ascorbic acid and

citric acid. In aqueous solution the rate of hydrolysis and esterification is typically pH dependent. In aqueous solution, the degradation of ipratropium bromide exhibits a pH-rate minimum at pH 3.5. Acid equivalent is given in units of normality which defines a **pH range** equivalent to **2.0-4.7** in an aqueous system (see pages 10-12). Table 2 (page 16) shows a formulation comprising ipratropium bromide, ethanol, water and ascorbic acid. Ascorbic acid is added in an amount of from **0.00015 to 5.0 mg/ml** and the optimum pH level of the formulation is maintained at a range of from 2.0 to 4.7.

Jager does not specifically teach adding edetic acid or a salt thereof.

Bozung et al teach medicament compositions based on anticholinergic compounds which have a long-lasting effect and betamimetics, which have a long-lasting effect, processes for their production and their use in the therapy of respiratory ailments, especially **COPD** (col. 1, lines 11-16). **Tiotropium bromide monohydrate** is the preferred anticholinergic (col. 5, lines 51-55). The medicaments for inhalation are dissolved in an **aqueous or ethanolic solution**, wherein solvent mixtures of ethanol and water are also suitable. Other adjuvants, such as preservatives, e.g. benzalkonium chloride in concentration range of 8 to 12 mg/100 ml are added. Complex formers like **EDTA**, **citric acid, ascorbic acid** can be added. The medicament is present in an amount of from **0.001 to 5%** (see col. 6, line 39 to col. 7, lines 17-40).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations comprising anticholinergics such

as tiotropium and ipratropium, solvent, and acid with a pH level of from 2.0 to 4.7 as taught by Jager by implementing the acid of Bozung et al to prepare a similar formulation with acceptable and suitable stability. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

**Claims 38-49, 51, 52, 81-92, 94 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al or alternatively over Jager et al in view of Bozung et al as applied to claims listed above, and further in view of Weston et al (WO 9114468).**

Freund et al, discussed above, lacks specific teachings on the inhalation device.

Jager et al in view of Bozung et al, discussed above lack specific disclosure on the inhalation device.

Weston et al discloses a metered dose inhaler which incorporates metering means for metering a quantity of fluid, and the atomizing means is provided by a mechanical break up device through which the metered quantity of fluid is passed to atomise it when it is subject to said increase in pressure (page 7, lines 5-9). For dispensing a spray of an aqueous solution of a medicament for inhalation into lungs, the droplet size is desirably less than 10 micrometers, typically 2 to 6 micrometers.

Weston also discloses that very high pressures can be generated in the pump cylinder or pressure and nozzle orifice diameters can be used, for example up to 100 micrometers, typically greater than 30 to 50 micrometers. The preferred pressures are from 50 to 400 bar, and more preferably from 100 to 350 bar with nozzle orifice of from 1 to 12 micrometers (page 12, lines 1-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have utilized the preparation of Freund et al. or Jager et al and Bozung et al, by incorporating it in a device suitable for such preparations and because it is made simpler in design and cheaper to produce and suited to its function, as taught by Weston et al.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/068,134 (US 20050147564). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent comprising a tiotropium salt in a concentration range of between 0.0005% and 5% by weight, a steroid, a solvent such as water or ethanol and a preservative, wherein the formulation has a pH of from 2.0 to 3.5. The claims of instant application are drawn to a similar preparation. The difference is that the steroid is not required.

This is a provisional obviousness-type double patenting rejection.

Claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/392,558 (US 20040019073). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a tiotropium

salt in a concentration range of between 0.01 and 0.06 g per 100 ml of formulation, a solvent such as water and a preservative, wherein the formulation has a pH of from 2.7 to 3.1. The claims of instant application are drawn to a similar preparation. The difference is that the concentration range of tiotropium is slightly different.

This is a provisional obviousness-type double patenting rejection.

Claims **1-6, 38, 53-58 and 81** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/201,149 (US 20090088408). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent comprising a tiotropium salt, a steroid, a betamimetic and acceptable excipients and carrier. The claims of instant application are drawn to a similar preparation. The difference is that the steroid and the betamimetic are not required. The instant claims also require EDTA and water or ethanol/water as the solvent. However the claims of the reference employ the open language of “comprising” which allows for the other components to be included.

This is a provisional obviousness-type double patenting rejection.

Claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable

over claims of copending Application No. 11/006,940 (US 20050148562). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. Instant claims are drawn to formulations comprising an anticholinergic, preferably tiotropium and a second active agent such as a steroid. Formulations can be in a solution form and thus require a solvent. The preferred pH rang is from 2 to 7 (see e.g. claims 114 and 229). The claims of instant application are drawn to a similar preparation. The difference is that the second active agent such as steroid is not required.

This is a provisional obviousness-type double patenting rejection.

### *Response to Arguments*

Applicant's arguments filed 02/13/09 have been fully considered but they are not persuasive.

Applicant states that "Freund et al can not form the basis for an obviousness rejection because it teaches away from the presently claimed invention in two main aspects". Applicant continues that "the reduction in spray anomalies with low levels of edetic acid or edetic acid salt was not taught by Freund et al". Applicant refers to Table 1 on page 3 of Freund et al which shows a concentration of 50 mg/100 ml or more of EDTA in an ipratropium bromide solution yielded "0" spray anomalies as compared to tests run at lower levels of EDTA having between 2-6 spray anomalies. This is not persuasive because 1) Freund teaches addition of EDTA in a concentration range of from 10 to 100/100ml, which reads on the claimed range. 2) Freund et al '897 teach

very low levels of EDTA in similar formulations when the pH levels can be as low as 2. 3) Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

It is further noted that instant claims are drawn to a preparation (product) and are examined based on their components and not how the product functions.

Applicant, by referring to MPEP 2144.05 (III) regarding overlapping ranges, argues that "by showing the criticality and unexpected results of the claimed ranges" the obviousness can be overcome. This is correct, however not persuasive here because a criticality has not been shown. Table 1 of Freund et al reference, shows 8 tests performed on formulations containing 0, 0.1, 1, 50 and 75 mg/100ml EDTA. While formulations containing from 0 to 1 mg/100ml EDTA showed spray anomalies, the formulations comprising 50 or 75 mg/100ml EDTA did not show any spray anomalies. This test is not commensurate with Applicant's arguments because there is no tests performed on 10mg or 25mg which would be more comparable with 50mg and 0-25mg/100ml range that is claimed here. Thus Table 1 of Freund et al is not a proper comparison for the claimed range. Applicant is also referring to the data provided with their arguments here (an attachment filed with their arguments of 02/13/09) and believes that the said data shows criticality. This is not persuasive because the data does not show criticality or unexpected results. At pH levels of from 2.7 to 3.0, the number of sprays at 0-50mg/100g NaEDTA are not consistent with any conclusion. For example, at pH of 2.7 and 2.8, the formulations comprising 10 mg of NaEDTA showed 0

number of sprays with deviation, but at pH of 3.0, the formulations comprising 25mg showed 0 number of sprays with deviation. The results for the pH level of 2.7 (at 10 and 25mg) were very similar to those with a pH of 3.2, which is outside of Applicant's optimum pH level. On the other hand the number of sprays with deviation for the formulations at pH level of 2.8 and 25mg were the same as those for the pH of 3.1 and 50 mg and pH of 3.2 and 50 mg. In fact a formulation with a pH of 3.2 at 25 mg EDTA has a lower spray deviation levels (2.5%) than the formulation with pH of 2.8 and 25 mg EDTA (5.0%). Thus Applicants assertion that "An improvement of spray quality at lower pH values (2.7-3.0) in combination with lower NaEDTA concentrations (10 and 25 mg) is observed" is not found persuasive.

With regard to the rejection of claims over Jager et al in view of Bozung et al, Applicant argues that "Jager et al is directed to pharmaceutical solutions containing propellants, whereas the presently claimed invention is directed to specific *propellant-free* inhalable formulations". This is not commensurate with the scope of claims. Instant claims are **not** directed to a propellant-free formulation, there is no exclusion of the propellant and the claims employ the open language of "comprising" which allows for the inclusion of other components such as propellants.

Applicant argues that "the double patenting rejections are the only rejections remaining in this application. Thus, according to the MPEP provision above, terminal disclaimers are not necessary….". This statement is not correct. Claims remain rejected under prior arts of record and thus the claims are not in condition for allowance at this time and the said Double Patenting rejections remain pending.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
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